REMARKS:

Claims 9-18, and 21-38 are pending. Claims 1-8, 19, and 20 have been withdrawn. Claims 9-18 have been amended. Claims 21-38 are new. Neither the amendments to claims 9-18 nor new claims 21-38 add new matter. Support for the amendments to claim 9-18 may be found at paragraphs [0047], [0049], and [0050] of the published specification. Support for new claims 21-38 may be found at paragraphs [0047], [0048], [0049], [0050], [0069], and [0084] of the published specification.

I. 35 USC §112, first paragraph rejection

Reconsideration is requested of the rejection of claims 9-18 under 35 USC §112, first paragraph, for lack of enablement. Amended claim 9 is directed to a method of decreasing cell proliferation. The method comprises contacting a eukaryotic cell comprising a wild-type MetAP2 with a composition comprising an isolated polynucleotide. The polynucleotide encodes a variant eukaryotic MetAP2 that lacks aminopeptidase activity, comprises a eukaryotic translation domain, and possesses dominant negative MetAP2 activity. The dominant negative activity of the variant MetAP2 decreases the proliferation of the cell.

To satisfy the enablement requirement, a claimed invention must be enabled by the specification so that a person skilled in the art can make and use the invention without undue experimentation.[1] Claim 9 is enabled because the present application teaches one of ordinary skill in the art how to make and use a variant eukaryotic MetAP2 with dominant negative activity in the manner recited in the claim.

*a. The specification teaches how to **make** a dominant negative MetAP2*

The present application teaches that "[d]ominant negative variants of MetAP2 ... comprise, preferably, a translation domain and an inactive

[1] In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988); MPEP 2164.01

aminopeptidase or catalytic domain."[2] The specification further teaches how to make a variant of MetAP2 with both a translation domain and an inactive aminopeptidase domain. For example, as stated in the Declaration under 37 C.F.R. §1.132 of Dr. Yie-Hwa Chang ("Chang declaration"), "[o]ne of skill in the art would be able to follow the teachings of the specification to create a MetAP2 variant that lacks aminopeptidase activity but comprises a translation domain, and thereby create a MetAP2 variant that possesses dominant negative activity."[3]

A translation domain is defined by the specification as a "domain that mediates the association of any molecule to a ribosome, translation initiation factor or any component of the translational machinery of a cell."[4] These domains "have been found in several proteins,"[5] and consequently, are known in the art. In relation to MetAP2, the specification specifically provides the sequence of four translation domains from MetAP2 proteins derived from four widely divergent organisms: human, mouse, rat and yeast (SEQ ID Nos: 1, 2, 15, or 3 respectively). These sequences then, can be used to predict the translation domains in other eukaryotic MetAP2 proteins using methods well known in the art, such as BLAST searches.[6] Therefore, the specification enables an ordinary person skilled in the art to make a variant MetAp2 that comprises a translation domain.

The specification also teaches how to make a MetAP2 with an inactive aminopeptidase or catalytic domain. Specifically, the specification highlights that "the conserved histidine of the catalytic domain [histidine 231 … of human …, mouse…or rat… MetAP2, or histidine 174 … of yeast MetAP2…] may be replaced with another amino acid."[7] "His^{174} or His^{231} is strictly conserved ***in all*** *MetAPs sequenced to date*." Additionally, the specification highlights that "given

[2] Paragraph [0053] of the published specification.
[3] See Attachment A, Chang declaration, at point 2(c).
[4] Paragraph [0034] of the published specification.
[5] Paragraph [0051] of the published specification.
[6] Paragraph [0055] of the published specification.
[7] Paragraph [0047] of the published specification.

the unique molecular structure of histidine, … its position within a beta sheet comprising the active site of the catalytic domain and its *complete conservation* in all MetAP2s sequenced to date, this histidine serves an important role in the aminopeptidase function of MetAP2." Therefore the skilled artisan would understand that to create a variant eukaryotic MetAP2 with an inactive aminopeptidase, the artisan need only mutate the conserved histidine, which is conserved in all MetAP2s sequenced to date. The specification further provides the skilled artisan with sequences to four different MetAP2 proteins.[8] Furthermore, examples 1 and 3 detail how to mutate His^{231} or His^{174}.

Moreover, the specification provides additional ways of creating a MetAP2 with an inactive aminopeptidase or catalytic domain. Specifically, "any variant form of MetAP2 which abolishes the active site pocket, abolishes fumagillin binding sites, and/or amino acids involved in the coordination of a cobalt ion…"[9] will lack aminopeptidase activity. The active site pocket, the fumagillin binding sites, and the amino acids involved in the coordination of a cobalt ion are known to those skilled in the art.[10] Furthermore, the specification lists the "amino acids that contact fumagillin," namely, "according to the numbering system of human MetAP2 (SEQ ID NO:12), Phe^{219}, Leu^{328}, Ile^{3}, His^{339}, Tyr^{444} and Leu^{447}." Additionally, the specification provides the amino acids "involved in the coordination of Co^{2+} ions," namely, "according to the numbering system of SEQ ID NO:12, Asp^{251}, Asp^{262}, His^{331}, Glu^{364} and Glu^{459}." Therefore, one skilled in the art, using known algorithms[11], would be able to determine which amino acids of a eukaryotic MetAP2 contact fumagillin or are involved in the coordination of a cobalt ion, and subsequently, can make a MetAP2 that lacks aminopeptidase activity.

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[8] The sequences of yeast, rat, mouse, and human MetAp2s may be found in figure 1 and in the sequence listing (SEQ ID Nos: 6, 7, 8, 9, 10, 11, 16, and 18).
[9] Paragraph [0048] of the published specification.
[10] For instance, the crystal structure of MetAP2 complexed to fumagillin was published in 1998. Science. 1998 Nov 13;282(5392):1324-7. "Structure of human methionine aminopeptidase-2 complexed with fumagillin."
[11] Such algorithms are detailed in paragraph [0055] of the published application.

Consequently, because the specification not only teaches one, but more than one method of how to make a variant MetAP2 with a translation domain and an inactive aminopeptidase or catalytic domain, the specification teaches how to make a MetAP2 with dominant negative activity. Furthermore, the specification provides an assay to determine if a variant MetAP2 has dominant negative activity, as detailed in Examples 1 and 3.

*b. The specification teaches how to **use** a dominant negative MetAP2 in a method to decrease cell proliferation*

The specification specifically provides that dominant negative MetAP2 "inhibits the cell proliferation-promoting effect of wild-type MetAP2 and [is] therefore useful for inhibiting ... cell proliferation..."[12] Furthermore, the specification provides examples of using a dominant negative MetAP2 to decrease cell proliferation in two *widely divergent* eukaryotic cell types, namely yeast (Example 1) and human (Example 3) cells. As stated in the Chang declaration,

> [t]hese two organisms represent the spectrum of eukaryotic complexity. Hence, a skilled researcher would reasonably conclude that if a dominant negative variant of MetAP2 inhibits cell proliferation in both a yeast cell and a human cell [as shown in Examples 1 - 3], a dominant negative variant of MetAP2 would also inhibit cell proliferation in a eukaryotic organism that falls between yeast and humans in complexity.[13]

Moreover, Examples 1 - 3 utilize different ways of contacting the cell with the polynucleotide encoding the dominant negative MetAP2. Example 1 utilizes a lithium-acetate method of transformation, while Example 3 utilizes a viral transformation system. Additionally, the specification provides direction on how to determine if a dominant negative MetAP2 "would be effective in the inhibition of

[12] Paragraph [0053] of the published application.
[13] Chang declaration, at point 2(e).

growth of a particular cell," and provides examples of how to determine if a dominant negative MetAP2 is actually effective.[14] Therefore, the specification enables one of skill in the art to contact a eukaryotic cell with a polynucleotide encoding a dominant negative MetAP2 to decrease cell proliferation.

In view of the fact that the specification teaches a skilled artisan to make and use the invention defined by claim 9, applicants respectfully request withdrawal of the rejection based on §112, first paragraph for lack of enablement. Claims 10-18 depend from claim 9 and are sufficiently enabled for the reasons detailed above for claim 9.

Additionally, claim 10 requires that the eukaryotic cell is an endothelial cell. Example 3 of the specification teaches using a dominant negative MetAP2 variant in endothelial cells.[15] Therefore, claim 10 is enabled.

Also, claim 11 requires that the polynucleotide is part of a vector and is operably linked to a promoter. Examples 1 and 2 of the specification teach how to use different vectors and promoters in reference to contacting a eukaryotic cell with a polynucleotide encoding a dominant negative MetAP2 variant. Additionally, Claim 12 requires the vector to be an adenovirus vector, claim 13 requires the promoter to be a CMV promoter, and claim 14 requires both an adenovirus vector and a CMV promoter. Example 2 of the specification teaches an adenovirus vector and a CMV promoter. Indeed, the Office agrees that the specification teaches expressing a polynucleotide encoding a dominant negative MetAP2 variant "using an adenovirus vector and CMV promoter."[16] Therefore, claims 11-14 are enabled.

Claim 15 is limited to four eukaryotic variant MetAP2 amino acid sequences. The sequences are specifically provided in the specification. (See SEQ ID NO: 6, 7, 8, or 16.) Similarly, claim 17 is limited to four translation domain amino acid sequences. The sequences are specifically provided in the specification. (See SEQ ID NO: 1, 2, 3, or 15.) Claim 18 is also limited to four

[14] Paragraph [0073] of the published application.
[15] See paragraph [0133] of the published application.
[16] Office Action mailed February 12, 2007, at pg. 3

eukaryotic variant MetAP2 polynucleotide sequences. These sequences are also specifically provided in the specification. (See SEQ ID NO: 9, 10, 11, and 18). Therefore, claims 15-18 are enabled.

New claim 21 requires that the variant MetAP2 comprises a eukaryotic translation domain and lacks a functional active site pocket such that the variant MetAP2 lack aminopeptidase activity and possesses dominant negative MetAP2 activity. The crystal structure of MetAP2 was available at the time the application was filed, and therefore, one skilled in the art is enabled to make a variant MetAP2 by mutating one or more of the residues in the active site pocket defined in the crystal structure.[17]

New claim 22 requires that the variant MetAP2 comprises a eukaryotic translation domain, lacks the ability to bind fumagillin, and possesses dominant negative MetAP2 activity. The specification provides in paragraph [0048] the amino acids involved in fumagillin binding, and therefore, the specification enables one skilled in the art to make a variant MetAP2 by mutating one or more of these listed residues.

New claim 23 requires that H231 is mutated to abrogate fumagillin binding. As explained above, H231 is a conserved histidine found in every MetAP2 sequenced to date. Therefore, one of ordinary skill in the art would be able to mutate the conserved histidine to make a variant MetAP2. Consequently, the specification enables claim 23.

New claim 24 requires that the variant MetAP2 comprises a eukaryotic translation domain and lacks the ability to coordinate a cobalt ion such that the variant MetAP2 lack aminopeptidase activity and possesses dominant negative MetAP2 activity. At paragraph [0048] the specification provides the specific amino acids involved in coordinating a cobalt ion, and therefore, the specification enables one skilled in the art to make a variant MetAP2 by mutating one or more of these listed residues.

[17] Science. 1998 Nov 13;282(5392):1324-7. "Structure of human methionine aminopeptidase-2 complexed with fumagillin."

New claim 25 is directed to a method of decreasing cell proliferation. The method comprises contacting a mammalian cell comprising a wild-type MetAP2 with a composition comprising an isolated polynucleotide. The polynucleotide encodes a variant mammalian MetAP2 that lacks aminopeptidase activity, comprises a mammalian translation domain, and possesses dominant negative MetAP2 activity. The dominant negative activity of the variant mammalian MetAP2 decreases the proliferation of the cell. New Claim 25 is enabled for the same reasons detailed above with respect to claim 9. Additionally, new claim 25 is limited to a variant mammalian MetAP2. The specification provides the sequences of three different mammalian MetAP2 dominant negative variants, namely a mouse, rat, and human variant.[18] Therefore, claim 21 enables one of ordinary skill in the art to make and use a mammalian dominant negative MetAP2. Additionally, claims 26 –36 depend on claim 25, and are enabled for the same reasons detailed above.

New claims 37-38 are also directed to a method of decreasing cell proliferation. The method comprises contacting a yeast cell comprising a wild-type MetAP2 with a composition comprising an isolated and purified polynucleotide. The polynucleotide encodes a variant yeast MetAP2 that has the amino acid sequence of SEQ ID NO:8, and possesses dominant negative MetAP2 activity. The dominant negative activity of the variant yeast MetAP2 decreases the proliferation of the cell. New Claims 37-38 are enabled for the same reasons detailed above with respect to claim 9. Additionally, new claims 37-38 are limited to a variant yeast MetAP2 with the amino acid sequence of SEQ ID NO:8. The specification provides both the amino acid and nucleic acid sequences for a variant yeast MetAP2 (SEQ ID NO: 8 and 11). Therefore, claim 37 enables one of ordinary skill in the art to make and use a yeast dominant negative MetAP2. Additionally, claim 38 depends on claim 37, and is enabled for the same reasons detailed above.

[18] SEQ ID NO: 6, 7, 9, 10, 16, and 18

c. The Office incorrectly asserts that claims 9-18 are not enabled.

The Office, after evaluating the factors set forth in the Wands case, mistakenly asserts that a person with ordinary skill in the art would have to undergo undue experimentation to practice the invention. Specifically, the Office incorrectly identifies four limitations of claim 9 that are not enabled. Each is individually addressed below.

i. Claim 9 is enabled for eukaryotic MetAP2 dominant negative variants, not just yeast and human MetAP2 variants

The Office asserts that the application is enabling for a human and yeast MetAP2 variant, but not other organisms.[19] Specifically, the Office states that apart from the specific human and yeast dominant negative variants discussed in Examples 1-3, the specification "does not teach any other examples of variant polynucleotides coding for a dominant negative MetAP2..."[20] And that the "art is unpredictable" with regard to which mutations would create a dominant negative MetAP2.[21] The Office is mistaken however.

Yeast and human MetAP2 have only 46% identity at the protein level, yet, by following the teachings of the specification, dominant negative variants of MetAP2 from both yeast and human organisms were created. These two widely divergent examples cover the spectrum of eukaryotic species (single-celled organisms to complex multi-celled organisms), and therefore, provide sufficient breadth to support claim 9. The Chang declaration explains:

> Yeast, a single-cell organism, is a simple eukaryote. In contrast, humans are a highly complex multi-cellular eukaryote. These two organisms represent the spectrum of eukaryotic complexity. Hence, a skilled researcher would reasonably conclude that if a dominant negative variant of MetAP2 inhibits cell proliferation in both a yeast cell and a human cell, a dominant negative variant of MetAp2 would

[19] Office Action mailed February 12, 2007 at pg. 4 and 6.
[20] Office Action mailed February 12, 2007 at page 4
[21] Office Action mailed February 12, 2007 at page 4.

> also inhibit cell proliferation in a eukaryotic organism that falls between yeast and humans in complexity.[22]

The MPEP §2164.02 states: "For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art… would expect the claimed genus could be used in that manner without undue experimentation." Therefore, in light of the Chang declaration and two working examples from widely divergent eukaryotes, the specification enables eukaryotic MetAP2 dominant negative variants beyond human and yeast variants.

Furthermore, the specification provides the amino acid and nucleic acid *sequences* of dominant negative variant MetAP2 from **four** widely divergent eukaryotic organisms (yeast, human, rat, and mouse, SEQ ID NO: 6, 7, 8, 9, 10, 11, 16, and 18) Additionally, the specification specifically delineates, at paragraphs [0047] and [0048], which amino acids to mutate to make a variant MetAP2. Moreover, the specification details how to identify the amino acids to mutate in other eukaryotic MetAP2 sequences by comparing the sequences to the human MetAP2 sequence. Additionally, the specification notes that one of the important amino acids, H231, is conserved in *every* MetAP2 sequenced to date. Therefore, following the teachings of the specification would allow one of ordinary skill in the art to create similar mutations in the identified amino acids and produce dominant negative variants in other eukaryotic organisms without undue experimentation. Hence, the method of claim 9 is enabled for eukaryotic MetAP2 dominant negative variants, not just human and yeast variants.

ii. Claim 9 is enabled for decreasing the proliferation of eukaryotic cells, not just yeast and human cells

The Office states that the application does not describe a "sufficient number of examples" to encompass decreasing the proliferation of *any* cell

[22] Chang declaration, at point 2(e).

type.[23] Amended claim 9, however, does not encompass *any* cell type, but is instead limited in two respects. First, amended claim 9 is limited to eukaryotic cells. Second, amended claim 9 is limited to cells that express wild-type MetAP2.

The specification provides explicit examples of decreasing proliferation in two different eukaryotic cells – yeast and human. The Chang declaration explains:

> [t]hese two organisms represent the spectrum of eukaryotic complexity. Hence, a skilled researcher would reasonably conclude that if a dominant negative variant of MetAP2 inhibits cell proliferation in both a yeast cell and a human cell, a dominant negative variant of MetAp2 would also inhibit cell proliferation in a eukaryotic organism that falls between yeast and humans in complexity.[24]

Furthermore, drug inhibitors of MetAP2 that are commonly known in the art, such as the cancer drug TNP-470, have been used to specifically inhibit MetAP2 and therefore decrease cell proliferation in many different cell types, as highlighted in paragraph [0071] of the application. These cell types include Kaposi's sarcoma cells, renal cells, brain cells, breast cells, cervical cells, and prostate cells.[25] In support of the foregoing assertion regarding the state of the art, the Chang declaration states "inhibition of MetAP2 was known to those skilled in the art to modulate the cell proliferation of ***multiple*** different cell types."[26] Hence, it is known in the art that specific inhibition of MetAP2 results in decreased cell proliferation in several different cell types. Therefore, the specification enables claim 9, such that decreasing proliferation in eukaryotic cells other than human and yeast cells with a variant MetAP2 does not require undue experimentation.

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[23] Office Action mailed February 12, 2007 at page 4
[24] Chang declaration, point 2(e).
[25] See Kruger And Figg. Expert Opin Invesitg Drugs (2000) 9(6):1383-96; paragraph [0010] of the published application.
[26] Chang declaration, point 2(a)

iii. Claim 9 is enabled for decreasing the proliferation of eukaryotic cells in vivo as well as in vitro.

The Office claims that the specification is enabled for *in vitro* use, but not for *in vivo* use.[27] The applicants, however, have provided an example of *in vivo* use. Example 1 details decreasing yeast cell proliferation by contacting a yeast cell with a variant MetAP2. Yeast are single-celled organisms. Therefore, by necessity, the experiments were performed *in vivo* in yeast.

Additionally, Example 3, which describes decreasing human cell proliferation, was performed using human HUVE cells. These cells are an accepted model for *in vivo* angiogenesis. The Chang declaration explains:

> in vitro studies using Human Vascular Endothelial (HUVE) cells are recognized in the art as a model system for studying cell proliferation, and studies using HUVE cells are recognized in the art as correlating with in vivo events.[28]

Indeed, the preliminary testing on such now approved drugs as TNP-470 were performed in these cells.[29] TNP-470 has anti-angiogenic effects that stem from inhibiting MetAP2. These effects were initially tested in HUVE cells. See, for example, Br J Cancer (1994) 69(2):212-6 and J Pharmacol Toxicol Methods (2000)43(1):15-24.

The MPEP states that if the art recognizes a particular model as "correlating to a specific condition [here, angiogenesis], then it should be accepted as correlating unless the examiner has evidence that the model does not correlate." In the present case, the examiner provides no evidence that this model does not correlate. Therefore, the *in vivo* HUVE model should be accepted as correlating, and consequently, enabling for decreasing *in vivo* cell proliferation.

iv. Claim 9 is enabled for use with different vectors as well as adenovirus vectors

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[27] Office Action mailed February 12, 2007 at page 3.
[28] Chang declaration, point 2(b)
[29] See Br J Cancer. 1994 Feb;69(2):212-6; J Pharmacol Toxicol Methods. 2000 Jan-Feb;43(1):15-24.

The Office states that claim 9 is not enabled for use with "any vector." As an initial matter, applicant would like to clarify that claim 9 *does not* contain vectors as a claim limitation. Instead, claim 9 focuses on *contacting* a eukaryotic cell with an isolated and purified polynucleotide. The specification provides two examples of how to contact a cell. Example 1 specifically shows lithium-acetate transformation as a method of contacting, while example 2 specifically shows the use of an adenovirus vector as a method of contacting. Additionally, paragraph [0069] of the specification provides multiple other vectors that may be appropriate for contacting a cell with a dominant negative MetAP2 variant. Therefore, claim 9 is enabled for use with more than an adenovirus vector. This is the case, contrary to the Examiner's assertion, even if the claimed genus includes some inoperable embodiments. As stated by the Board in Ex parte Cole:

> ...claims are addressed to the person of average skill in the particular art. Compliance with § 112 must be adjudged from that perspective and not in a vacuum. It is always possible to theorize some combination of circumstances which would render a claimed composition or method inoperative, but the art-skilled would assuredly not choose such a combination.[30]

II. 35 USC §102(b) rejection

Reconsideration is requested of the rejection of claims 9-18 under 35 USC §102(b) in view of the journal article authored by Griffith et al.[31]

Amended claim 9, as described above, is directed to a method of decreasing cell proliferation. The method comprises contacting a eukaryotic cell that expresses wild-type MetAP2 with a composition comprising an isolated polynucleotide, wherein the polynucleotide encodes a variant eukaryotic MetAP2 that lacks aminopeptidase activity, comprises a eukaryotic translation domain, and possesses dominant negative MetAP2 activity. The claim requires that the dominant negative activity of the variant eukaryotic MetAP2 decreases the proliferation of the cell.

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[30] *Ex parte Cole*, 223 U.S.P.Q 94, 95-96 (Bd. Pat. App. 1983).
[31] PNAS USA 95:15183-15188

In contrast, Griffith et al. discloses that the "covalent modification of His231 [of MetAP2] by fumagillin, ovalicin, and TNP-40 serves to irreversibly block the active site of MetAP2, preventing substrate binding and catalysis."[32] The authors of the Griffith reference engineered several mutations in the active site of MetAP2, and expressed the mutated proteins using a baculovirus expression system. Importantly, Griffith et al. used fumagillin, or a similar drug, to impede cell proliferation. Griffith et al. did not disclose, mention, or suggest, inhibiting cell proliferation by anything other than a fumagillin-like drug. Specifically, Griffith et al. does not disclose decreasing cell proliferation with a dominant negative MetAP2.

For a reference to anticipate a claim under 35 U.S.C. §102, the reference must teach "*each and every* element as set forth in the claim" in a single prior art reference.[33] Claim 9 requires that the dominant negative activity of the variant MetAP2 decreases the proliferation of the cell. The Griffith reference does not teach, either explicitly or impliedly, decreasing cell proliferation with a dominant negative MetAP2. Griffith et al. only disclose using fumagillin or a similar drug to modify cell proliferation. Because each and every element of claim 9 is not disclosed by the cited reference, the reference does not anticipate claim 9.

The Office agrees that "[the Griffith] reference does not specifically teach that the variant of MetAP2 inhibits cell proliferation."[34] The Office continues, however, stating that the "*claimed MetAP2 variant* appears to be the same as the prior art MetAP2 variant," and that "in the absence of evidence to the contrary, the burden is on the applicant to prove that the *claimed* ***product*** is different from those taught by the prior art." Claim 9, however, is *not* directed to a product. Claim 9 is directed to a *method* of decreasing cell proliferation through the dominant negative activity of a variant MetAP2. Amended claim 9 requires, as a *claim limitation*, that the variant MetAP2 with dominant negative activity

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[32] Griffith et al., pg. 15188
[33] *Verdegaal Bros. V. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987); See Also MPEP §706.02.
[34] Office Action mailed February 12, 2007 at page 7.

decreases cell proliferation. This, as the Office acknowledges, is not disclosed by the Griffith article. Therefore, the Griffith article cannot anticipate claim 9.

Moreover, dependant claims 10-18 each incorporate the aforementioned element of claim 9 and are likewise not anticipated by the Griffith article for the same reasons outlined above.

In addition, dependent claim 10 requires that the eukaryotic cell is an endothelial cell. The Office incorrectly states that the Griffith article "teaches expression of wild type and said mutant gene (polynucleotide) in endothelial cells." Rather, Griffith et al. only teach expression of the variant MetAP2 in a baculovirus expression system, intended only for protein harvesting.[35] Once purified, the MetAP2 variants were used *only* for *in vitro* studies by Griffith et al.[36] The bovine aortic endothelial cells that the Office highlights on "p.15184, col. 1, 3rd paragraph,"[37] were used to test the engineered fumagillin derivatives, *NOT* the MetAP2 variants.[38] Therefore, the Griffith et al. article does not anticipate claim 10, because the Griffith article does not disclose contacting an endothelial cell with a variant MetAP2 polynucleotide.

Dependent claim 12 also requires that the polynucleotide encoding the variant MetAP2 is part of an adenovirus vector. Relatedly, dependent claim 13 requires that the polynucelotide is operably linked to a CMV promoter. The Griffith article does not disclose or teach an adenovirus vector or a CMV promoter. Therefore, the Griffith article does not anticipate claims 12 or 13. Moreover, dependent claim 14 incorporates the limitations of claim 12 and claim 13, and therefore, is also not anticipated by the Griffith article for the same reasons cited above in reference to claims 12 and 13.

Furthermore, dependent claim 15 is limited to four eukaryotic variant MetAP2 amino acid sequences (SEQ ID Nos: 6, 7, 8, and 16). Similarly,

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[35] See Griffith et al., pg. 15186, column 2, first full paragraph: "[W]e proceeded to produce all three mutants in baculovirus-driven High Five insect cells and purified them to near homogeneity by Talon affinity chromatography."
[36] *Id.*
[37] Office Action mailed February 12, 2007 at page 7.
[38] Griffith et al., pg. 15185, columns 1 and 2

Dependent claim 18 is limited to four eukaryotic variant MetAP2 nucleotide sequences (SEQ ID Nos: 9, 10, 11, and 18). The Griffith article does not disclose or teach SEQ ID Nos: 6, 7, 8, 9, 10, 11, 16, or 18. Therefore, the Griffith article does not anticipate claims 15 or 16.

New claims 21 –24 are dependent on claim 9, and therefore incorporate each of the limitations of claim 9, namely, that the variant MetAP2 decreases the proliferation of the cell. Consequently, the Griffith article does not anticipate claims 21-24 for the reasons stated above.

Additionally, claim 21 requires that the variant MetAP2 lacks a functional active site pocket. Griffith et al. do not teach a variant MetAP2 that lacks a functional active site pocket. Consequently, the Griffith article does not anticipate claim 21, because the Griffith article does not teach or disclose every limitation of claim 21.

Also, claim 24 requires that the variant MetAP2 lacks the ability to coordinate a cobalt ion, such that the variant MetAP2 lacks aminopeptidase activity. Griffith et al. do not teach a variant MetAP2 that lacks the ability to coordinate a cobalt ion. Consequently, the Griffith article does not anticipate claim 24, because the Griffith article does not teach or disclose every limitation of claim 24.

New claims 25-38 also each require that the variant MetAP2 decreases the proliferation of the cell, similar to claims 9-18 and 21-24. Therefore, Griffith et al. does not anticipate new claims 25-38 for the same reasons discussed above in relation to claim 9.

Additionally, new claim 26, similar to claim 10, requires that the eukaryotic cell is an endothelial cell. As discussed above, the Griffith reference does not disclose contacting an endothelial cell with a variant MetAP2 polynucleotide, and therefore does not anticipate new claim 26.

New claim 28 further requires that the mammalian cell is a human cell. Griffith et al. does not disclose contacting a human cell with a variant MetAP2 polynucleotide. Therefore, the Griffith reference does not anticipate claim 28, because the Griffith article does not teach or disclose every limitation of claim 28.

Also, new claim 29, similar to claim 21, requires that the variant MetAP2 lacks a functional active site pocket. As discussed above, Griffith et al. do not teach a variant MetAP2 that lacks a functional active site pocket. Consequently, the Griffith article does not anticipate claim 29, because the Griffith article does not teach or disclose every limitation of claim 29.

New claim 33, similar to claim 15, is limited to four eukaryotic variant MetAP2 amino acid sequences (SEQ ID Nos: 6, 7, 8, and 16). As discussed above, the Griffith article does not disclose or teach SEQ ID Nos: 6, 7, 8, or 16. Therefore, the Griffith article does not anticipate claim 33, because the Griffith article does not teach or disclose every limitation of claim 33.

New claim 35, similar to claim 24, requires that the variant MetAP2 lacks the ability to coordinate a cobalt ion, such that the variant MetAP2 lacks aminopeptidase activity. As discussed above, Griffith et al. do not teach a variant MetAP2 that lacks the ability to coordinate a cobalt ion. Consequently, the Griffith article does not anticipate claim 35, because the Griffith article does not teach or disclose every limitation of claim 35.

New claim 37 requires the eukaryotic cell to be a yeast cell, and that the variant MetAP2 have the amino acid sequence of SEQ ID NO:8. The Griffith article does not disclose contacting a yeast cell with a variant MetAP2 polynucleotide, nor does the Griffith article disclose the sequence of SEQ ID NO:8. Therefore, the Griffith article does not anticipate claim 37, because the Griffith article does not teach or disclose every limitation of claim 37.

New claim 38 incorporates the limitations of claim 37, and additionally requires that the variant MetAP2 polynucleotide have the sequence of SEQ ID No:11. The Griffith article does not disclose SEQ ID NO:11, and therefore, does not anticipate claim 38 because the Griffith article does not teach or disclose every limitation of claim 38.

Consequently, the applicants respectfully request withdrawal of the §102(b) rejection of claims 9-18 in light of Griffith et al.

III. 35 USC §103 rejection

Reconsideration is requested of the rejection of claims 9-18 under 35 USC §103(a) in view of the Griffith article in combination with US patent No. 6,110,744 (Fang et al.; hereinafter the '744 patent).

Griffith et al., as discussed above, discloses that the known MetAP2 inhibitor, fumagillin, functions by covalently modifying the H^{231} amino acid of human MetAP2. Griffith et al. did not disclose, mention, or suggest, inhibiting cell proliferation by anything other than a fumagillin related drug. Specifically, Griffith et al does not disclose decreasing cell proliferation with a dominant negative MetAP2.

The '744 patent discloses adenovirus vectors comprising, in part, a CMV promoter. The vectors may be used to produce an infectious, conditionally replication-defective adenovirus particle. The '744 patent does not disclose variants of MetAP2. Similar to the Griffith reference, the '744 patent also does not disclose decreasing cell proliferation with a dominant negative MetAP2.

Three criteria must be present to establish a prima facie case of obviousness.[39] First, the prior art reference(s) must teach or suggest all the claim limitations.[40] Second, there must be some suggestion or motivation in the knowledge generally available to one of ordinary skill in the art to modify the reference.[41] Third, there must be a reasonable expectation of success.[42] Not one of these three criteria is satisfied by the Griffith reference alone or in combination with the '744 patent.

Neither Griffith et al. nor the '744 patent teach or suggest every claim limitation of amended claim 9. Specifically, neither Griffith et al. nor the '744 patent discloses or suggests a method of decreasing cell proliferation with a variant MetAP2 that has dominant negative activity. Instead, the Griffith patent focuses only on using a fumagillin-like drug to modulate cell proliferation.

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[39] See MPEP §2143
[40] *In re Royka*, 490 F.2d 981 (CCPA 1974)
[41] *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991)
[42] *In re Merck & Co., Inc.*, 800 F.2d 1091 (Fed. Cir. 1986)

Consequently, because neither cited reference teaches or suggests every claim limitation of amended claim 9, the Griffith reference and the '744 reference, whether taken individually or combined, do not render claim 9 obvious.

Additionally, there is no suggestion or motivation in the knowledge generally available to one of ordinary skill in the art to modify the Griffith reference or the '744 patent such that claim 9 is rendered obvious. The Griffith reference focuses on the mechanism of a known inhibitor of MetAP2 function. Importantly, in order to modulate cell proliferation, the Griffith reference teaches that you have to use a fumagillin-like drug. The reference discloses that a MetAP2 protein with alanine instead of histidine at position 231 lacks catalytic activity. But this is markedly different from dominant negative activity. For a comparison of the differences between a catalytically inactive protein, a drug-inactivated protein, and a dominant negative protein when added to an assay comprising wild-type protein, see Table 1.

Table 1:

Added element	**Total amount of protein**	**Does wild-type protein posses an active catalytic site?**	**Measured result of wild-type protein activity**
Catalytically inactive protein	Increases	Yes	Stays the same
Drug capable of inactivating protein	Stays the same	No	Decreases
Dominant Negative Protein	Increases	Yes	Decreases

If a catalytically inactive protein is added to an assay that comprises wild-type protein, then one skilled in the art would expect that you would merely increase the total protein in the cell without effecting the measured result of the

wild-type protein's activity. In stark contrast, the addition of a dominant negative protein to an assay that comprises wild-type protein not only increases total protein level, but *decreases the measurable enzymatic activity of the wild-type protein, in a dose-dependant fashion.*

Furthermore, if a fumagillin-like drug is added to an assay comprising wild-type MetAP2 protein, the drug will block the active site of the protein, therefore decreasing the measured result of wild-type protein activity. However, if you add a dominant negative MetAP2 to an assay comprising wild-type MetAP2 protein, you will not affect the wild-type protein's active site, but you will decrease the activity of the wild-type MetAP2. In the present invention, this is because the dominant negative MetAP2 is bound to ribosomes, excluding the wild-type MetAP2, and therefore impeding the wild-type MetAP2 protein's activity.

The Griffith article focuses on the first two rows of Table 1, namely a catalytically inactive MetAP2 and a drug capable of inactivating MetAP2 (fumagillin). The differences highlighted in Table 1 between a catalytically inactive protein and a dominant negative protein show that, to one of skill in the art, a catalytically inactive protein is not necessarily and inevitably a dominant negative protein. The Chang declaration states

> A skilled researcher in the art knows that a catalytically inactive variant is not synonymous with a dominant negative variant, and that it would not be obvious, likely, or intuitive that a catalytically inactive variant would possess dominant negative activity. Stated another way, dominant negative activity does not necessarily and inevitably flow from a catalytically inactive variant.[43]

Therefore, there was no suggestion or motivation in the knowledge generally available to one of ordinary skill in the art to modify the Griffith reference so as to use a variant MetAP2, with dominant negative activity, to modulate cell proliferation.

Lastly, there would have been no reasonable likelihood of success to modify the Griffith article to use the catalytically inactive MetAP2 to modulate cell

[43] Chang declaration, point 2(d)

proliferation, because, as shown in Table 1, with a catalytically inactive protein, one of skill in the art would have predicted no change wild-type protein activity, and therefore, no change in cell proliferation.

In summary, neither the Griffith article nor the '744 patent disclose the claim limitation of claim 9-18 and 21-27 of decreasing cell proliferation with a dominant negative MetAP2. Additionally, there would have been no motivation or suggestion in the knowledge generally available to one skilled in the art to use the catalytically inactive MetAP2 as a dominant negative MetAP2. Furthermore, there would have been no reasonable likelihood of success because one skilled in the art would not expect a catalytically inactive protein to modulate wild-type protein activity, and therefore, cell proliferation. Consequently, not one of the three requirements for a prima facie case of obviousness is met by the Griffith reference, either alone or in combination with the '744 reference. Therefore, these references can not render the present claims obvious and applicants respectfully request withdrawal of the §103(a) rejection of claims 9-18 in light of Griffith et al. and the '744 patent.

IV.CONCLUSION

In light of the foregoing, applicants request entry of the claim amendments, withdrawal of the claim rejections, and solicit an allowance of the claims. The Examiner is invited to contact the undersigned attorney should any issues remain unresolved.

Respectfully submitted,
Polsinelli Shalton Flanigan Suelthaus PC

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By: /Rebecca Riley-Vargas/
Rebecca Riley-Vargas, Reg. No. 60,046
110 South Fourth Street, Suite 1100
St. Louis, MO 63102
Phone – 314-889-8000
Fax – 314-231-1776
Patent Agent